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WO 2004/016269 A1

(54) Title: USE OF VINCA ALKALOYDS, TAXANE, CRYPTOPHYCINE, EPHITOLINE OR ELEUTHEROBINE FOR TREATING ALZHEIMER

(57) Abstract: The present invention relates to medicaments that are useful in the prevention, halting or reversal of Alzheimer's disease progression through the stabilisation of at least one cytoskeletal and/or microtubule stabilising compound.

USE OF VINCA ALKALOYDS, TAXANE, CRYPTOPHYCINE, EPHITOLINE OR ELEUTHEROBINE FOR TREATING ALZHEIMER

The present invention relates to medicaments that are useful in the prevention, halting or reversal of Alzheimer's Disease progression in mammals and these medicaments are cytoskeletal and/or microtubule stabilisers.

Alzheimer's Disease (AD) is a chronic debilitating and devastating neurodegenerative disorder, that gives rise to failure of all but the most primitive cognitive functions. As AD is predominately present in patients over the age of 65, this particular disease will become a massive problem for society as society's average age increases in the medium term.

AD is diagnosed by the presence in brain tissue of extra cellular plaques that are mainly composed of β–amyloid (Aβ) that is produced by proteolytic processing of a longer transmembrane protein, the Alzheimer Precursor Protein (APP), see Figure 1.

Importantly however, there also exists intracellular aggregations of a microtubule binding protein called *Tau* that has been aberrantly modified in a number of ways, the most common being hyper-phosphorylation. These modifications induce *Tau* to aggregate into insoluble helical rods termed Paired Helical Filaments (PHF).

Currently two main theories exist in the field of AD research that explain the aetiology and progression of this disease. The first and most widely accepted is the amyloid cascade hypothesis. This hypothesis argues that there is a strong genetic influence, as in autosomal dominant disease mutations in the APP and presenilin genes give rise to the increased production of Aβ. Futhermore the extra cellular presence of Aβ (a neuro-toxin) in the brain tissue of AD patients explains the symptoms of AD caused by extensive neuronal cell death. This is supported by the observation that Down Syndrome patients who all have an additional copy of the APP gene, develop AD-like pathology from their early thirties. However, vaccines directed against Aβ were found to initiate a potentially lethal, inflammatory immune response in humans, which was not seen in the murine models.

The second theory involves the intracellular aggregation of the *Tau* protein. Abnormal phosphorylation of this protein, which plays a major role in intracellular protein trafficking, inhibits normal cellular functioning and causes eventual cell death. APP has not yet been implicated in this mechanism.

A recent finding by Roncarati et al (Proc Natl Acad Sci U S A. 2002 May 14;99(10):7102-7107) shows that the C-terminus of the APP protein plays a role in protein movement in cells via attachment to kinesin via the kinesin light chain (KLC) molecular motor, see Figure 2. The present inventors have developed a new, non-obvious unifying mechanism that incorporates the two above-mentioned hypotheses, explaining how APP and *Tau* are involved in AD progression.

It is already known that the APP protein is proteolytically cleaved by α, β and γ secretases (see Figure 1) and that α secretase cleaves APP towards the middle of Aβ sequence. This enzyme is of little consequence here. However β secretase, (Vassar et al Science, 1999 Oct, 286 (5440): 735-41), cleaves the last 100 amino acid residue of the APP C-terminus and this is further cleaved by the γ secretase to produce the Aβ peptide. The β secretase activity is known to be rate limiting step in this process. As yet the γ secretase is not characterised fully but the presenilin family of

proteins are known to be involved (Vassar R, J. Mol Neuroscience, 2001 Oct, 17(2):157-70).

It is proposed herein that the β and γ secretases are active in the detachment of intracellular vesicles from the molecular motors bound to the C-terminus of APP. Therefore in the event of abnormal APP degradation, leading to increased APP C-terminus levels in the cytoplasm, inevitable destabilisation of the intracellular trafficking system would eventually cause cell death. As the molecular motor bound to APP only binds to β-tubulin, the amount of available β-tubulin would decrease and the amount of available α-tubulin may increase or remain the same by biochemical negative and positive feed back mechanisms, respectively. Destabilisation of the microtubular network in the cell would give rise to increased levels of *Tau*, inducing PHF production by *Tau* hyper-phosphorylation. This combined with the presence of increased APP C-terminus would lead to higher levels of Aβ, as the γ secretase is not rate limiting. The cell would then export these Aβ residues into the extra-cellular space in order to reduce the intra-cellular concentration. As Aβ is neurotoxic, an inflammatory response is initiated leading to neurodegeneration and typical AD symptoms. However, the intracellular effects of Aβ on cellular metabolism, and more specifically vesicle trafficking is what this particular invention is concerned with.

With this in mind an object of the present invention is to stabilise the microtubular network in cells using known and/or new cytoskeletal stabilising compounds, so that the actions and effects of Aβ can be overcome. Some currently used anti-cancer drugs work by stabilising microtubules in cells, thereby lethally preventing mitosis, and we intend to show their ability to prevent, halt or reverse the biological activity of the Aβ peptide. Therefore, it is an object of the present invention to provide a medicament to prevent, limit or halt the progression of Alzheimer's Disease.

According to the present invention there is provided a medicament to prevent, limit or halt the progression of Alzheimer's Disease in patients, the medicament including at least one cytoskeletal-stabilising agent.

Cytoskeletal components of the cell are deemed to include actin filaments, microtubules and intermediate filaments.

Preferably the cytoskeletal agent is at least one microtubule stabilising agent.

Preferably the cytoskeletal agent is at least one actin stabilising agent.

Preferably the medicament is a combination of at least one cytoskeletal stabilising agent and/or at least one microtubule stabilising agent.

Preferably the medicament includes a Vinca alkaloid, a taxane, a cryptophycine, epothilone or an eleutherobine.

Preferably the medicament is an inhibitor of microtubule destablisers.

The invention thus provides the use of any of these agents in the preparation of a medicament for the treatment of Alzheimer's Disease.

Most preferably the medicament is or includes Taxol™.

Preferably the medicament inhibits the abnormal phosphorylation of the Tau protein. Abnormal phosphorylation includes hyperphosporylation of the Tau protein.

Preferably the medicament inhibits abnormal degradation of the Amyloid Precursor Protein and inhibits intra cellular build up of the Aβ peptide. Abnormal degradation of APP includes degradation of APP according to the amyloid pathway as opposed to the neutrophic pathway.

Preferably the medicament is specifically targeted to the brain. To target the medicament to the brain the medicament preferably is able to cross the blood brain barrier.

According to a further aspect of the present invention there is provided a medicament including Trk A, or an analogue thereof including a family member Trk B or Trk C.

According to another aspect of the present invention there is provided the use of Trk A, or an analogue thereof including a family member Trk B or Trk C in the preparation of a medicament for the treatment of Alzheimer's disease.

An agent includes a small molecule, compound, protein or part thereof.

Embodiments of the present invention will now be described, by way of example only, with reference to the accompanying drawings in which.

Figure 1 is a diagrammatic representation of the Amyloid Precursor Protein (APP);

Figure 2 is a diagrammatic representation of the APP protein of Figure 1, bound to kinesin, via the kinesin light chain, showing kinesin "walking" along a microtubule by selective

binding of the kinesin heavy chain to β tubulin submits of the microtubule;

Figure 3 is a Western Blot showing decreased levels of kinesin light chain C (60-70 kDa) in the presence of increasing expression levels of the Aβ peptide;

Figure 4 is a diagrammatic representation of the Western Blot of figure 4a showing decreased levels of kinesin light chain C (60-70 kDa) in the presence of increasing expression levels of the Aβ peptide;

Figure 5a is a Western Blot showing decreased levels of β tubulin (55kDa) and increasing levels of Amyloid β (4kDa) in the presence of increasing expression levels of the Aβ peptide;

Figure 5b is a diagrammatic representation of the Western Blot of figure 5a showing decreased levels of β tubulin (55kDa) and increasing levels of Amyloid β (4kDa) in the presence of increasing expression levels of the Aβ peptide;

Figure 6 is a diagrammatic representation of the Western Blot showing decreasing levels of TrkA (140kDa) in the presence of increasing expression levels of the Aβ peptide;

Figure 7 is a Western Blot showing increased levels of PHF - *Tau* in response to increased expression levels of Aβ peptide; and

Figure 8 is a Western Blot showing decreased levels of TRK A in response to a mutation of PS2.

As shown in Figure 1 the Amyloid Precursor Protein (APP) is a transmembrane protein that undergoes endoproteolysis by three proteases called α, β and γ-secretase. After complete processing of the APP protein, the β-amyloid 42 amino acid peptide is released intracellularly.

Figure 2 is a diagrammatic representation of APP binding to the kinesin light chain of the molecular motor kinesin. Kinesin "walks" selectively along a microtubule by binding selectively to β-tubulin via its kinesin heavy chain subunit.

Figure 3 is a picture of a representative Western Blot for kinesin light chain of protein extracts from cells expressing no Aβ peptide (lane 1); constitutively low expression of Aβ peptide cells (lane 2) and constitutively high expression of Aβ peptide cells (lane 3), i.e. transfected with the vector constitutively encoding the C100 peptide; wherein down regulation of kinesin light chain is obvious in lane 3.

Figure 4 is a drawing of a representative Western Blot for kinesin light chain of protein extracts from cells expressing no Aβ peptide (lane 1); constitutively low expression of Aβ peptide cells (lane 2) and constitutively high expression of Aβ peptide cells (lane 3), i.e. transfected with the vector constitutively encoding the C100 peptide; wherein down regulation of kinesin light chain is obvious in lane 3.

Figure 5b is another Western Blot for β-tubulin of the same cells as shown in Figure 4b where it is clear that the β-tubulin concentration decreases while amyloid β protein increases accordingly. Furthermore, as shown in figure 6, levels of a nerve growth factor receptor Trk A, carried by vesicles that use APP to connect to a molecular motor, are also decreased in a Aβ peptide concentration dependent manner.

As shown in figure 8, one of the primary neurotrophic molecules Trk A is decreased when a PS2 mutation is introduced in a cell line. The level of Trk A is also found to be decreased in cell lines having a PS1 mutation or a mutation in APP leading to an increase in the Aβ expression.

Trk A is a receptor which upon ligand binding is internalised and translocates from the cellular membrane to the nucleus of the cell. The presence

of Trk A in the nucleus causes the cell to continue to survive whereas a lack of Trk A in the nucleus promotes cell degradation. Trk A relies on cytoskeletal proteins for transport and thus disruption of the cytoskeletal proteins, as set out above, would decrease the level of Trk A being moved to the nucleus. As the movement of Trk A to the nucleus would be limited by disruption of cytoskeletal proteins, it is proposed to provide Trk A, family members Trk B or Trk C or an analogue thereof to the nucleus to promote cellular survival.

Figure 7 shows clearly increased levels of PHF-Tau due to the increasing levels of the Aβ peptide intracellularly.

Presenilin-mutated cell lines were looked at under the exact same conditions and show clearly that Aβ is involved in the manifestation of diseases arising from these mutations.

Components of the cell that bind to the Aβ peptide more specifically will be investigated using standard methods, including specific chemical cross linking of the C100 and/or Aβ peptide in the living cell or using cell free systems.

The possibility that the C100 peptide and/or Aβ may have some transcriptional control activity will be investigated by detecting its presence in the nucleus and its ability to complex with Tip60. The

protein profile of these cells will be analysed using high-resolution 2D gel electrophoresis and Q-TOF and/or MALDI TOF Mass Spec. The mRNA profile will be analysed using expression chips commonly known in this field of research.

The aim of the above experiments is to elucidate the complete mechanism of action of the C100 and Aβ peptides, so that the counter active activity of tubulin stabilising compounds like Taxol™ can be analysed.

An experiment in the process of being carried out is the use of magnetic beads with Anti- Aβ antibodies bound to them, which are then to be added to semi permeabilised cells that have been transfected with the constitutively expressed C100 peptide encoding vector, and these experiments will be repeated on control cells as well as the above transfected cells incubated with drugs like Taxol etc.

The constitutively expressed C100 peptide vector does not allow for the regulation or switching on and off of the expression of the C100 peptide described above.

The present inventors shall also investigate the role proteins like OP18 and Rb3 may play in the aetiology of AD, as they are known microtubule destabilisers proteins. The effect of microtubule destabilisers in an essential part of further investigation.

Various modifications can be made without departing from the scope of the invention, for example, ways of negating the effect of microtubule destabilisers would elicit the same effect as medicaments to stabilise cytoskeletal proteins. Suitable inhibitors of microtubule destabilisers would be known to those in the art.

Claims

1. A medicament to prevent, limit or halt the progression of Alzheimer's Disease the medicament including at least one cytoskeletal-stabilising agent.

2. A medicament as claimed in claim 1 to prevent, limit or halt the progression of Alzheimer's Disease the medicament including at least one inhibitor to microtuble destabilisers.

3. A medicament as claimed in claim 1 or 2 wherein the medicament is a combination of at least one cytoskeletal stabilising agent and/or at least one microtubule stabilising agent.

4. A medicament as claimed in claim 1 to 3 wherein the medicament includes a Vinca alkaloid, a taxane, a cryptophycine, epothilone or an eleutherobine.

5. A medicament as claimed in claim 1 to 4 wherein the medicament inhibits the abnormal phosphorylation of the Tau protein.

6. A medicament as claimed in claim 1 to 5 wherein the medicament inhibits abnormal degradation of the Amyloid Precursor Protein and inhibits intra cellular build up of the Aβ peptide.

7. A medicament to prevent, limit or halt the progression of Alzheimer's Disease the medicament

including Trk A, or an analogue thereof including a family member Trk B or Trk C.

7. A medicament as claimed in any preceeding claim wherein the medicament is specifically targeted to the brain.

8. Use of at least one cytoskeletal stabilising agent and/or at least one microtubule stabilising agent in the preparation of a medicament for the treatment of Alzheimer's Disease.

9. Use of at least one inhibitor of microtubule destabilisers in the preparation of a medicament for the treatment of Alzheimer's Disease.

10. Use of Trk A, or an analogue thereof including a family member Trk B or Trk C in the preparatio of a medicament for the treatment of Alzheimer's Disease.

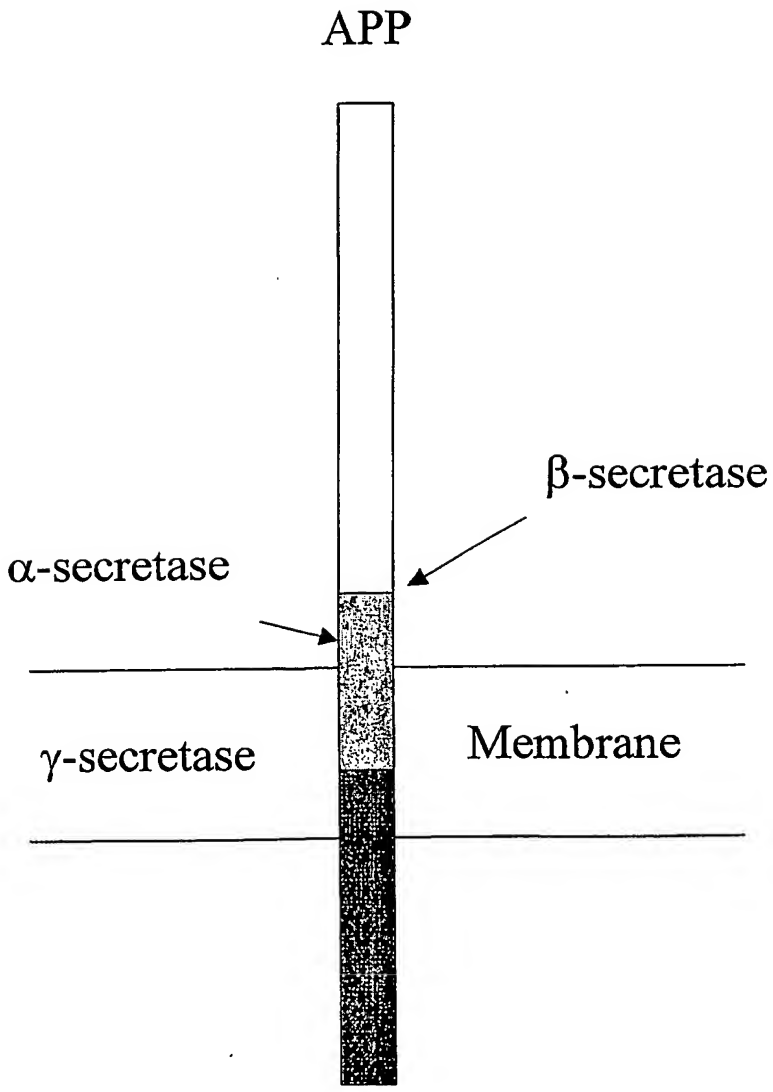


Figure 1

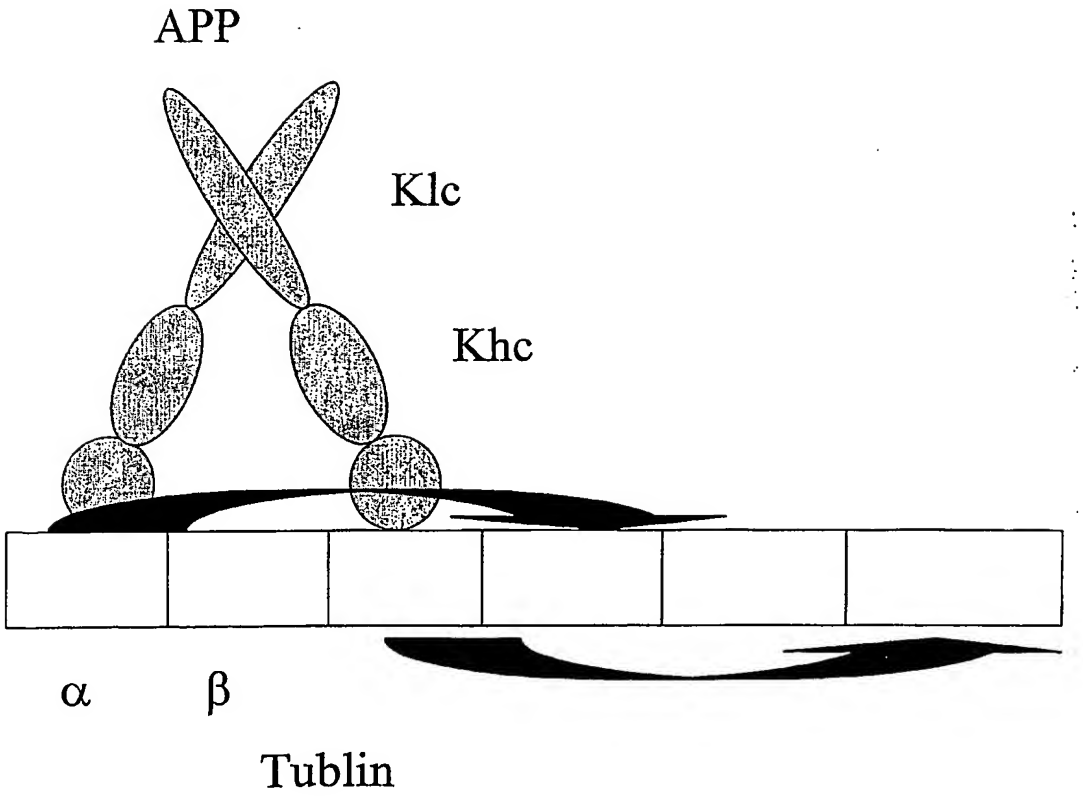
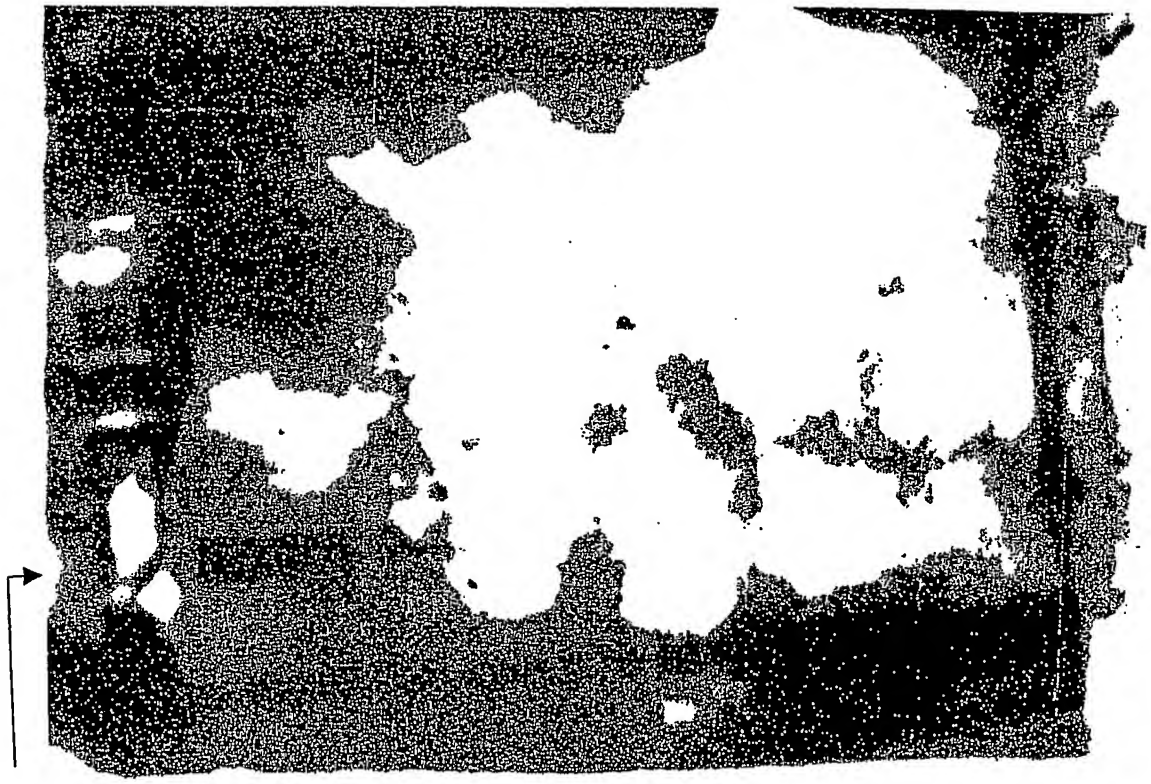


Figure 2

Figure 3



Kinesin

Figure 4

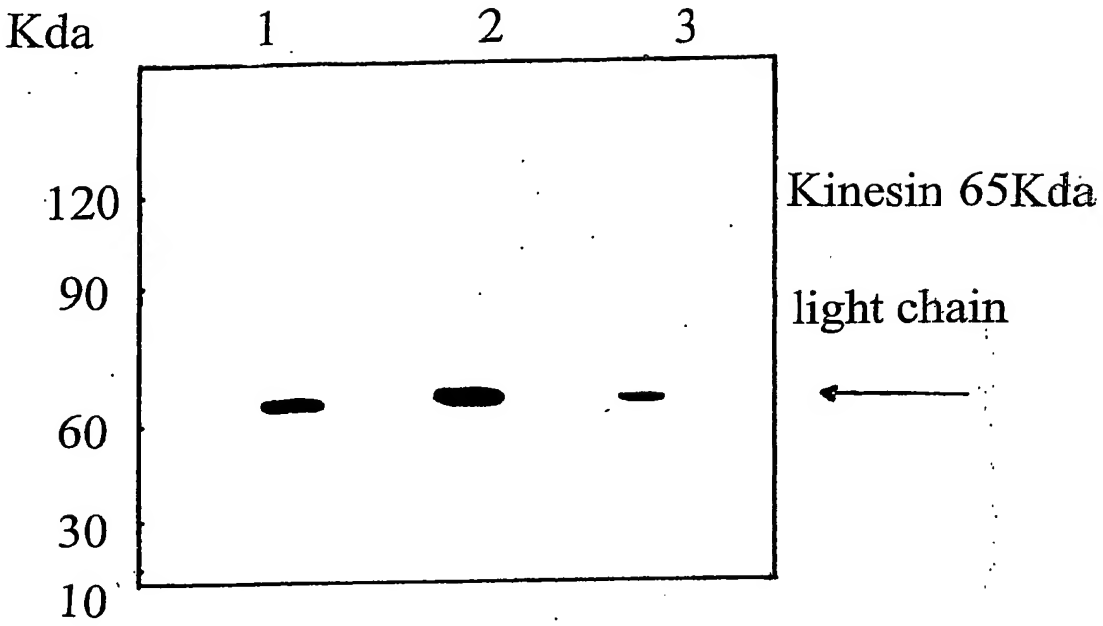


Figure 5a

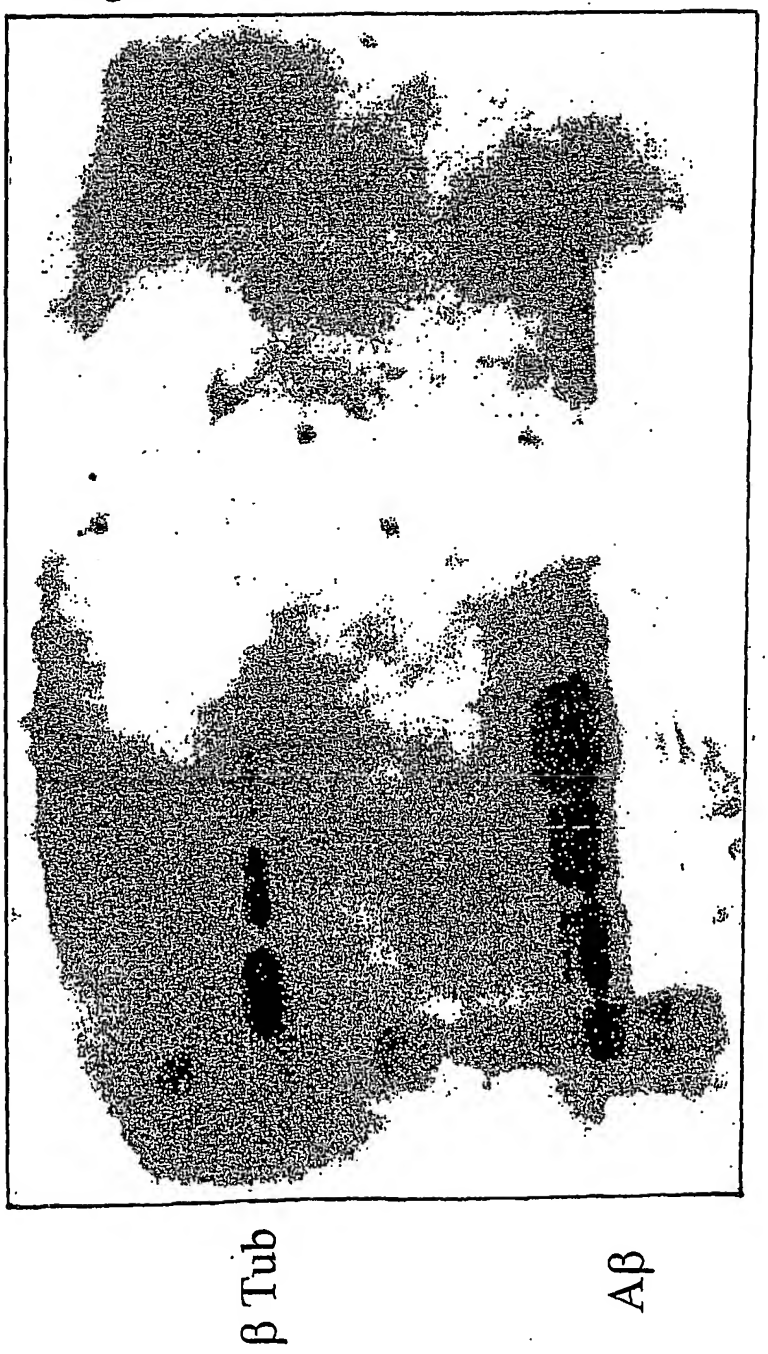


Figure 5b

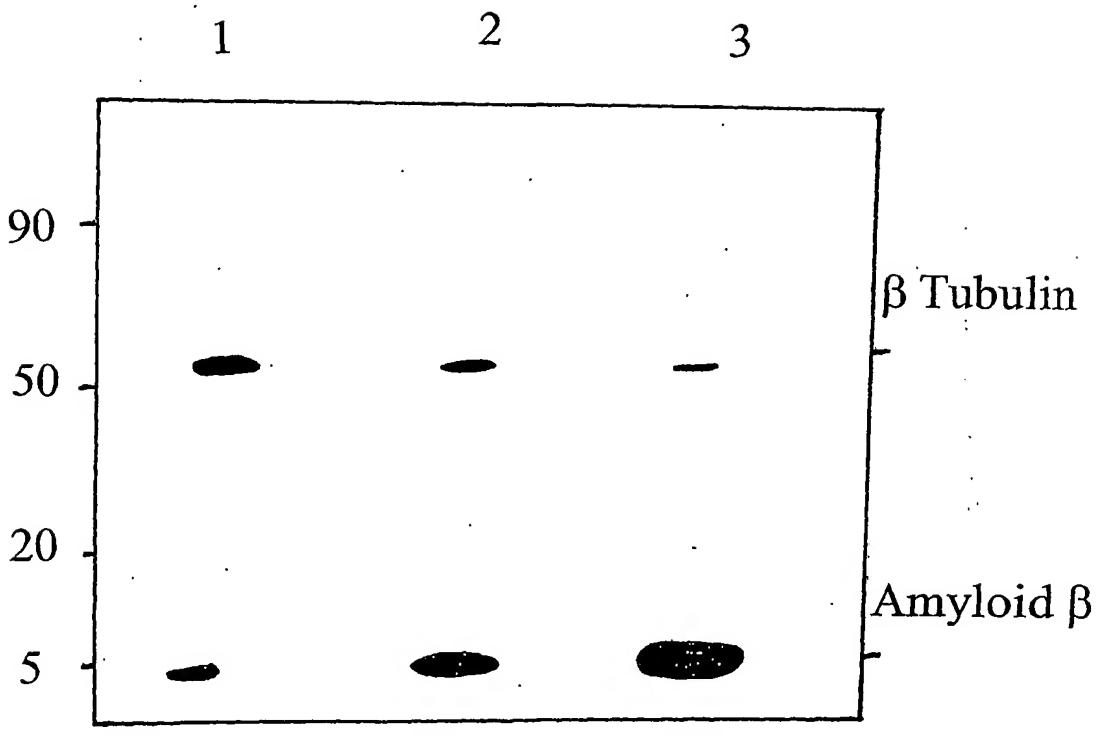


Figure 6

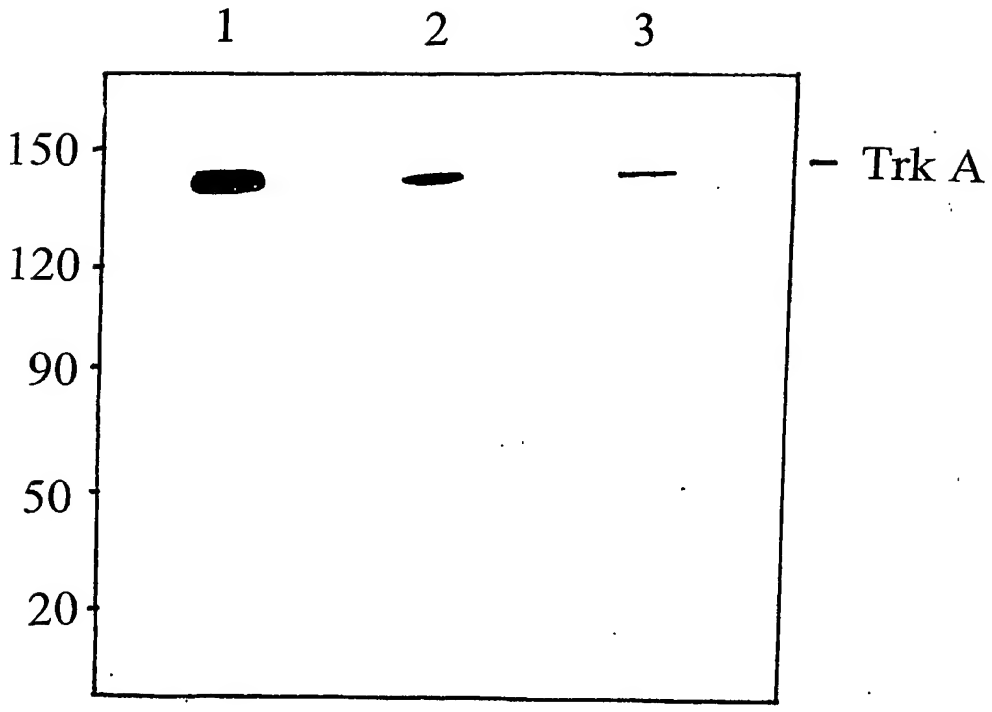


Figure 7

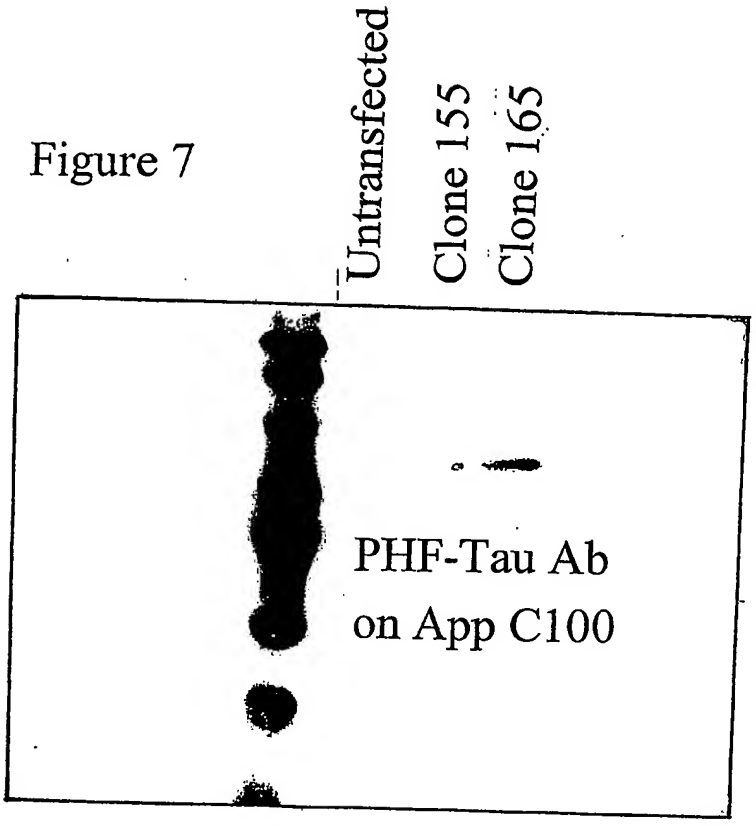
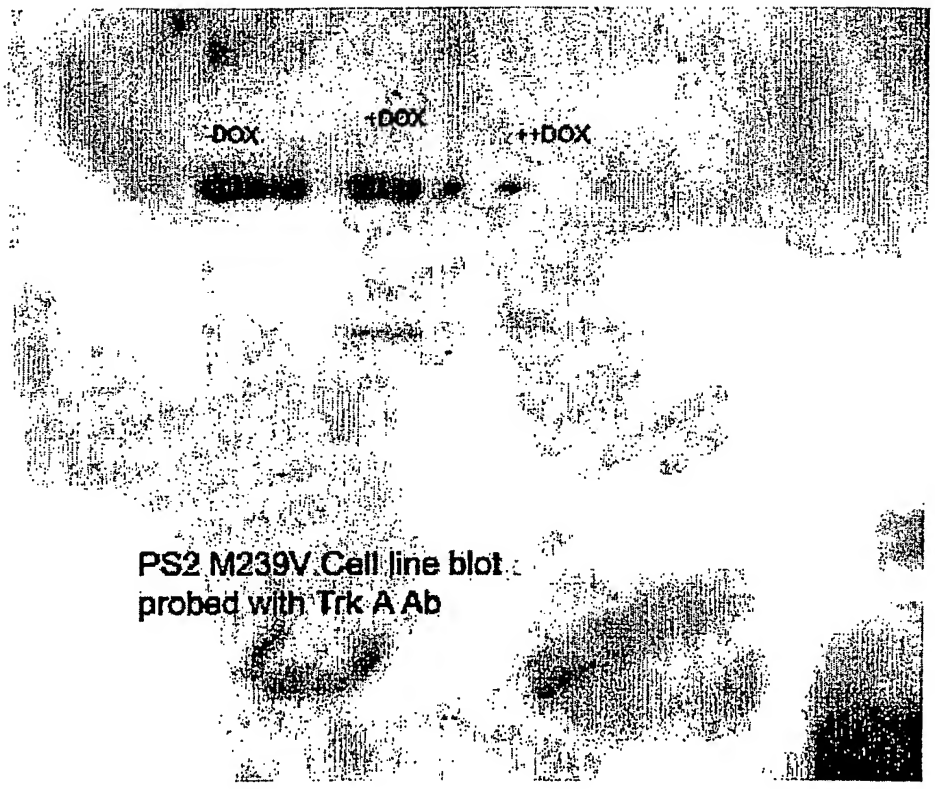


Figure 8



INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCI/GB 03/03601

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/475 A61K31/337 A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, MEDLINE, SCISEARCH, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LI G ET AL: "STABILZATION OF THE CYCLIN - DEPENDENT KINASE 5 ACTIVATOR, P35, BY PACLITAXEL DECREASES BETA - AMYLOID TOXICITY IN CORTICAL NEURONS." SOCIETY FOR NEUROSCIENCE ABSTRACT VIEWER AND ITINERARY PLANNER, vol. 2002, 2002, page Abstract No. 591.9 XP001172845 32nd Annual Meeting of the Society for Neuroscience;Orlando, Florida, USA; November 02-07, 2002 the whole document --- -/--	1,2,4-6, 9-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the International search report
10 November 2003	17/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bonzano, C

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCI/GB 03/03601

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	POLLACK S J ET AL: "Natural product-derived small molecule activators of the Trk neurotrophin receptors" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 1, 2001, page 356 XP001172844 31st Annual Meeting of the Society for Neuroscience;San Diego, California, USA; November 10-15, 2001 ISSN: 0190-5295 the whole document	
X	ADLARD PAUL A ET AL: "The effects of taxol on the central nervous system response to physical injury" ACTA NEUROPATHOLOGICA, vol. 100, no. 2, August 2000 (2000-08), pages 183-188, XP001173124 ISSN: 0001-6322 page 183, column 2, line 12 - line 30 page 184, column 1, paragraph 3 page 187, column 2, paragraph 3	1,2,4-6, 8-11
X	FURUKAWA K ET AL: "A microtubule stabilizing compound, taxol, attenuates neuronal vulnerability of tau mutations in FTDP-17" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 1, 2001, page 922 XP001173123 31st Annual Meeting of the Society for Neuroscience;San Diego, California, USA; November 10-15, 2001 ISSN: 0190-5295 the whole document	1,2,4-6, 9-11
A	BOISSIÈRE F ET AL: "Trk neurotrophin receptors in cholinergic neurons of patients with Alzheimer's disease." DEMENTIA AND GERIATRIC COGNITIVE DISORDERS. SWITZERLAND 1997 JAN-FEB, vol. 8, no. 1, January 1997 (1997-01), pages 1-8, XP008024311 ISSN: 1420-8008 page 7, column 2, paragraph 2	7
P,X	RICE ANTONIE ET AL: "Overcoming the blood-brain barrier to taxane delivery for neurodegenerative diseases and brain tumors." JOURNAL OF MOLECULAR NEUROSCIENCE, vol. 20, no. 3, 2003, pages 339-343, XP008024299 ISSN: 0895-8696 (ISSN online) page 339, column 1, line 1 -column 2, line 2 page 343, column 1, paragraph 1	8

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INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/GB 03/03601

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	KIDD P M: "A review of nutrients and botanicals in the integrative management of cognitive dysfunction." ALTERNATIVE MEDICINE REVIEW: A JOURNAL OF CLINICAL THERAPEUTIC. UNITED STATES JUN 1999, vol. 4, no. 3, June 1999 (1999-06), pages 144-161, XP008024312 ISSN: 1089-5159 page 151, column 1, paragraph 4 -column 2, paragraph 2 ---	
A	LEMAIRE LAURENT ET AL: "Magnetic resonance imaging of the neuroprotective effect of Xaliproden in rats" INVESTIGATIVE RADIOLOGY, vol. 37, no. 6, June 2002 (2002-06), pages 321-327, XP008024309 ISSN: 0020-9996 abstract ---	
X	EP 0 870 510 A (LILLY CO ELI) 14 October 1998 (1998-10-14) page 2, paragraph 1 claim 17 ---	1-8
A	CINEL B ET AL: "Solid-state and solution conformations of eleutherobin obtained from X-ray diffraction analysis and solution NOE data" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 41, no. 16, April 2000 (2000-04), pages 2811-2815, XP004195677 ISSN: 0040-4039 page 2811, paragraph 1 ---	4
A	GIANNAKAKOU PARASKEVI ET AL: "A common pharmacophore for epothilone and taxanes: Molecular basis for drug resistance conferred by tubulin mutations in human cancer cells" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 97, no. 6, 14 March 2000 (2000-03-14), pages 2904-2909, XP002189845 ISSN: 0027-8424 page 2904, column 1, paragraph 1 abstract -----	4

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 03/03601

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3,5, and 8,9,10 encompass a genus of compounds defined only by their function (cytoskeletal stabilising agent and microtubule destabiliser), wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Therefore this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope not fully possible (Articles 5, 6 PCT).

Claims 4-6,8 relate to an extremely large number of possible compounds (taxanes, Vinca alkaloids, cryptophycines, eleutherobines). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). It is not clear to which compounds exactly the protection is sought. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Present claim 8 (if corrected numeration applies) relates to a compound or a combination of compounds defined by reference to a desirable characteristic or property, namely the specific targeting to the brain. Nothing is said in the application, to explain how such a characteristic is achieved. In the present case, the claim so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the composition by reference to its pharmacocynetic profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds taxol, vincristine vinblastine, cryptophycine, epothilone and eleutorobine, and to trk for the treatment of Alzheimer disease.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an

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international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/GB 03/03601

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0870510 A	14-10-1998	AU 7104798 A	11-11-1998
		EP 0870510 A2	14-10-1998
		WO 9846193 A2	22-10-1998